DECLARATION OF THOMAS D. MADDEN, PH.D.

I, Thomas D. Madden, Ph.D., declare as follows:

1. I currently hold the position of Senior Director, Technology Development & Licensing, at Inex Pharmaceuticals Corp., located in Burnaby, British Columbia, Canada, an assignee of U.S. Patent Application No. 10/782,738, entitled "Compositions and Methods for Treating Lymphoma."

2. I have read and am familiar with the above-identified patent application and the Office Action mailed December 23, 2005 with respect to this application. I submit this Declaration for the purpose of providing additional evidence that the liposomal vincristine kits claimed in the instant application are not obvious in light of the references cited in this Office Action. More specifically, I submit that the skilled artisan would not have been motivated to produce the liposomal vincristine kits claimed in the above-identified patent application in light of these references.

3. Specifically, the teachings of U.S. Patent No. 5,741,516 (Webb) and U.S. Patent No. 5,762,957 (Mehlhorn) would not motivate the skilled artisan to produce the presently claimed kit. Webb provides no motivation to produce kits comprising unencapsulated vincristine. Instead, Webb states that drug-loaded liposomes may be packaged or lyophilized for later use.

4. In addition, the motivations the Examiner alleges are provided by Mehlhorn, namely reduced drug leakage and reduced liposome degradation, were not considered to be problems associated with the sphingomyelin-based liposomes present in the liposomal vincristine formulations of Webb or the presently claimed kits. As described in Webb, sphingomyelin-based liposomes have increased drug retention as compared to liposomes produced using other conventional lipids. In addition, sphingomyelin is more stable and less susceptible to hydrolysis than other lipids conventionally used in liposomes. Thus, neither of these references would motivate the skilled artisan to produce a kit comprising separate vials of sphingomyelin-based liposomes and unencapsulated vincristine.

5. Furthermore, I submit that subsequent to the filing of the above-identified patent application, Inex conducted stability studies on the liposomal formulation of

vincristine sulfate described in Webb, and found that this formulation does not have preferred commercial stability of the encapsulated vincristine. Studies evaluating vincristine purity in liposomal vincristine formulations maintained at 5° C for up to 36 week showed that even by 24 weeks, vincristine degradation products are present above the US Pharmacopoeia and European Pharmacopoeia limits in some samples (range 4.8 – 6.6%). At 36 weeks, samples contained more than 10% degradation products. Accordingly, the shelf-life of the liposomal vincristine formulation described in Webb is considered less than desirable for certain commercial applications.

5. However, the liposomal vincristine kit claimed in the above-identified application has an increased shelf-life as compared to the liposomal vincristine formulations described in Webb. This kit provides an aqueous solution of vincristine sulfate that meets or exceeds regulatory requirements (*i.e.*, less than 6.0% vincristine-related products) for up to 2 years. The vincristine sulfate is then loaded into the liposomes before being administered to the patient. Therefore, the presently claimed liposomal vincristine kit provides an economically viable shelf-life, thereby enhancing the commercial attributes of sphingomyelin-based liposomal vincristine.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Date May 23rd 2006

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